UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 2 4 1993

010119

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Tribufos (DEF®), Rat Combined Chronic/Oncogenicity Study

TO: Bruce Sidwell PM-53
Reregistration Branch
Special Review and Reregistration Division (H7508C)

FROM: Robert P. Zendzian Ph.D.
Senior Pharmacologist
Toxicology Br II
Health Effects Division (H7509C)

THROUGH Karl Baetcke Ph.D.
Chief
Toxicology Br II
Health Effects Division (H7509C)

Compound; Tribufos (DEF®) Tox Chem #864

Registration #074801 Registrant; Miles

MRID #423351-01 DP barcode; D179536

Action Requested

Review the following study;

Technical grade tribufos (DEF®): A chronic feeding study in the Fischer 344 rat, W.R. Christenson, Miles Inc. Study No 88-271-AA, Report # 102675, May 1, 1992, MRID 423351-01

Core Classification Guideline

Conclusion
Doses tested 0, 4, 40 and 320 ppm. No oncogenic response. Compound related effects are listed below at the lowest dose at which they were observed: (Males, Females 12months)

4ppm
decreased plasma cholinesterase M&F

40ppm
decreased weight gain M
decreased RBC count, Hemoglobin, hematocrite. M&F
decreased cholosterol, calcium M
decreased RBC cholinesterase M&F
320ppm
decreased weight gain F
increased food consumption M&F
terminal opthamological exam; cataract, lens opacity, corneal opacity, corneal neovascularization, iritis/uveitis M&F
terminal ERG; unrecordable M&F
decreased Totprotein, globulin, cholesterol, calcium M&F
increased BUN M&F
decreased brain cholinesterase M&F
Adrenals; vacular degeneration 12m M&F
Eyes; retinal atropy 12m M&F
Small intestine; autolysis, vacoular degeneration 12m M&F
Eyes; retinal atropy, uveitis, cataract, neovascularization 24m M&F
Optic nerves; atropy 24m M&F
Small intestine; autolysis, vacoular degeneration, hyperplasia 24m M&F

Recommendations

1. No action is requested from the Registrant at this time.

2. The HED Carcinogenicity Peer Review Committee will be requested to reevaluate their classificiaton of tribufos as a class C oncogen in light of the results of the rat oncogenicity study.

3. Considering the spectrum of significant toxic effects exhibited by tribufos (organophosphate delayed neurotoxicity, metabolite toxicity, toxicity to the eye and oncogenicity), HED will develop a recommendation of special review of the compound.

Discussion

Tribufos (DEF®) [S,S,S-Tributylphosophorotrithioate] is an organophosphate cholinesterase inhibiting compound used as a defoliant on cotton. The rat study reviewed here completes the oncogenic assesment of tribufos. No evidence of an oncogenic response was observed in the rat study. However, the mouse oncogenicity study showed a statistically significant incidence of adenocarcinoma/carcinoma in the small intestine in both sexes, hemangiosarcoma in the liver of the males and alveolar/brochiolar neoplasia in the lungs of the females all at the high dose (MRID 411710-01). The information on tribufos was presented to the HED Peer Review Committee for an evaluation and clasification of the oncogenicity of the compound. The Committee considered tribufos meet the criteria for a class C oncogen and recommended that a Q_1* be determined. Since the

in life portion of the rat oncogenicity study had been completed, it was recommended that the Q_1^* not be determined until the results of the rat study were obtained and had been presented to the Committee.

The results of the rat study, and additional data developed since the initial Peer Review of tribufos, will be presented to the Committee for formal evaluation. However, considering the nature of the additional data, it is not expected to change the Comittiee's conclusions. Therefore, determination of a Q_1^* for tribufos will be requested from the statistical group.

Attachments
DER
1-liner

Data Evaluation Report 010119

Compound Tribufos (DEF)

Citation
Technical grade tribufos (DEF®): A chronic feeding study in the Fischer 344 rat, W.R. Christenson, Miles Inc. Study No 88-271-AA, Report # 102675, May 1, 1992, MRID 423351-01

12/31/92

Reviewed by Robert P. Zendzian Ph.D.
Senior Pharmacologist
Health Effects Division

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Compound related effects are listed at the lowest dose at which they were observed: (Males, Females 12months)
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decreased cholosterol, calcium M
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320ppm
decreased weight gain F
increased food consumption M&F
terminal opthamological exam; cataract, lens opacity, corneal opacity, corneal neovascularization, iritis/uveitis M&F
terminal ERG; unrecordable M&F
decreased Totprotein, globulin, cholesterol, calcium M&F
increased BUN M&F
decreased brain cholinesterase M&F
Adrenals; vacular degeneration 12m M&F
Eyes; retinal atropy 12m M&F
Small intestine; autolysis, vacoular degeneration 12m M&F
Eyes; retinal atropy, uveitis, cataract, neovascularization 24m M&F
Optic nerves; atropy 24m M&F
Small intestine; autolysis, vacoular degeneration, hyperplasia 24m M&F

Materials

Technical grade Tribufos
colorless to pale yellow clear liquid
Batch No; 85R26-39
98.7%

From Mobay Ag Chemicals Division

Male and female Fischer [CDF(F-344)/BR] rats from Charles River (380 males and 380 females)

Experimental design

Number of rats per dose group and observation/sacrifice regimen

Dose (ppm)	Onco 24	Cronic 12	Neurotoxic 12	Neurotoxic 24	(month of sacrifice)
0	50/50	20/20	10/10	10/10	
4	50/50	10/10	10/10	10/10	
40	50/50	10/10	10/10	10/10	
320	50/50	20/20	10/10	10/10	

males/females

Dosing

Test material was provided in the feed at nominal concentrations of 0, 4, 40 amd 320 ppm. Test material was dissolved in corn oil at the appropriate concentration to provide nominal concentrations when added to the diet at 1% by weight corn oil. Diet was prepared weekly and stored in the freezer.

Test material was analyzed for qualitative and quantitative composition and for stability in the freezer. Homogeneity, concentration and stability of test material in the diet was determined at the 4 and 320 ppm concentrations.

Observations

Body weights and food consumption were determined weekly. Clinical observations were recorded daily, a detailed physical examination performed weekly and body tempeature determined weekly.

Prior to dosing and just prior to sacrifice, opthalmic exams were conducted on all animals on study. "Just prior to termination, electroretinographic examinations (ERGs) were performed on the eyes of selected two-year animals and all surviving two-year neurotoxicity animals."

Clinical Pathology

"Blood was drawn for clinical pathology determinations from 20 rats/sex/level of the two-year sacrifice group after approximately 3, 6, 12, 18 and 24 months on study; to the extent possible, the same rats were used throughout the study."

Clinical chemistry

alanine aminotransferase
albumin
alkaline phosphatase
aspartate aminotransferase
brain cholinesterase(terminal)
calcium
chloride
cholesterol
creatine kinase
creatinine
direct bilirubin
erythrocyte cholinesterase
gamma-glutamyl transpeptidase
globulin
glucose (fasting)
lactic dehydrogenase
phosphorous
plasmacholinesterase
potassium
sodium
total bilirubin
total protein
triglyceride
urea nitrogen
uric acid

Hematology

RBC count
hemoglobin
WBC count
MCH
MCHC
MCV
hematocrite
platelet count
differantial count
reticulocyte count

Urinalysis

ketones
pH
bilirubin
occult blood
Glucose
protein
urobilinogen
clarity
color
specific gravity
microscopic sediment

Termination

Gross pathological examinations were performed on all animals at termination. The following tissues were collected and examined microscopically. Asterixed organs were weighed.

adrenals*
aorta
bone
  femur
  rib
  sternum
bone marrow
brain*
  cerebrum-midbrain
  cerebellum
  medulla/pons
cervix
cliteral gland
epididymis
esophagus
mammary gland
muscle
nerve
  optic
  sciatic
ovaries*
pancreas
parathyroid
physical identifier
pituitary
preputial gland
prostrate
rectum
salivary gland
skin

exorbital lac/gland
eyes
gross lesions
harderian gland
heart*
joint, fem/tib
kidneys*
larnyx
liver*
lungs*
lymph node
  cervical
  mesenteric
  lumbar
  thoracic
skull
small intestine
  duodenum
  ileum
  jejunum
spinal cord
  cervical
spleen*
stomach
testicles*
thymus*
thyroid
trachea
urinary bladder
uterus

The neurotoxicity groups were anesthetized and the nervous tissue fixed in situ by perfusion with fixative. "In the neurotoxicity groups, after perfusion, only the following tissues were collected for microscopic examination: brain, spinal cord, and both hind limbs (after exposure of the sciatic nerves and their branches). In addition, eyes and optic nerves were collected from two-year sacrifice neurotoxicity rats for possible ultrastructural examination, per protocol amendment. All of the above tissues from neurotoxicity aminals were fixed in universal fixative."

Statistical analysis was performed on numerical data utilizing a computer.

Results

Test substance confirmed that the material was 97.7% pure and freezer stable. Stability, homeogeneity and concentration analysis in the test diets produced a mean revcovery of 96.5%. The AI was stable and homogeneous in the test diet with concentrations that did not differ significantly from nominal.

Body weight and survival data of the 24 month animals, at four week intervals, are presented in tables A and B. Statistically significant depression of growth was observed in both sexes at 320 ppm throughout the study. In the males at 40 ppm, significant depression was observed at the majority of intervals while in the females depression was observed in only a few intervals. No effect on body weight was observed at 4 ppm. A slight but not significant decrease in survival was observed in both sexes at 320 ppm. Survival exceeded 50% in all experimental groups.

Mean food consumption and mean intake of test compound are presented in Table AI-MEAN from the report. On a g/kg

basis, food consumption was slightly increased in both sexes at 320 ppm. No differences from controls was observed at 4 or 40 ppm. Mean intake of test material (AI) was 0.0, 0.2, 1.8 and 16.8 mg/kg/day for the males and 0.0, 0.2, 2.3 and 21.1 mg/kg/day for the females.

Compound related signs of toxicity observed mainly at the high dose consisted of increased incidences of paleness, eye opacity, rough coats, rashes and raised zones, urine staining and diarrhea. No treatment-related effect was observed on body temperature.

No compound-related lesions were observed in the eyes of the 12 month sacrific animals by ophthamological examination. At termination the following lesions were observed;

		Dose ppm			
		0	4	40	320
Posterior, subcapsular or complete cataract	M	5/40	5/38	5/34	27/30*
	F	4/35	6/28	6/31	15/30*
Lens opacity	M	6/40	4/38	3/34	8/30
	F	9/35	8/28	5/31	20/30*
Diffuse or focal corneal opacity	M	21/40	20/38	26/34	31/30*
	F	20/35	27/28*	20/31	31/30*
Corneal neovascularizaton	M	2/40	6/38	1/34	15/30*
	F	11/35	7/28	4/31	19/30*
Iritis and/or uveitis	M	3/40	5/38	7/34	31/30*
	F	3/35	5/28	5/31	29/30*

* $p \leq 0.05$

The incidence of bilateral unrecordable ERGS at termination was as follows;

		Dose ppm			
		0	4	40	320
Two year oncogenicity group	M	0/15	2/9	0/15	11/13*
	F	1/16	2/16	0/13	7/8*
Two year neurotoxicity group	M	1/5	1.5	1/5	8/8*
	F	1/7	3/8	0/7	7/7*

* $p \leq 0.05$

Hematology

Significant ($p \leq 0.05$) treatment related decreases in erythrocytes, identified by decreases in count, hemoglobin and hematocrite were observed at 40 and 320 ppm in both sexes at days 84, 175 and 350. At day 539 hemoglobin was decreased

in both sexes with an increase in count such that derived values indicated decreased erythrocite volume (size). At 714 days (termination) increases in count and hematocrite (males and hemoglobin and hematocrite (females) indicated a compensatory increase in number and size of the erythrocites.

Clinical chemistry

Decreased total protein, globulin, cholesterol and calcium were observed in both sexes at 320 ppm throughout the study and cholesterol and calcium in the males at 40 ppm.

Blood urea nitrogen was increased at 320 ppm in males and females in most samples.

ALP and ALT activity was decreased in 40 ppm males and 320 ppm males and females in most samples.

Cholinesterase

Mean cholinesterase activity in the 24 year chronic/ oncogenicity animals is presented Table in CC2-SUM from the report. Plasma and RBC cholinesterase activity was significantly depressed ($p \leq 0.05$) at 40 and 320 ppm in both sexes throughout the study (84, 175, 350, 539 and 714 days). At 4 ppm plasma activity in males was significantly depressed at 539 and 714 days. At 4 ppm both acivities were significantly depressed in females at 84, 175 and 350 days and plasma activity was depressed at 714 days. Terminal brain cholinesterase activity (714 days) was significantly depressed at 320 ppm in both sexes.

Urinalysis

No apparent treatment-related effects were observed.

Gross pathology

Gross lesions that appeared to be treatment-related were relatively few. Abnormal consistancy and discoloration were observed in the small intestine of both sexes at 40 and 320 ppm, enlarged adrenal glands in both sexes at 320 ppm and opacity of the eye in males at 320 ppm.

Organ weights

Because of the decreased body weigh at 320 ppm in both sexes, absolute weights of all organs weighted were less than control and organ body weight ratios were increased. However some differences can be considered treatment related. Decreased absolute spleen and kidney weight in 40 and 320 ppm males at 24 months, increased absolute testicualr weight in 320 ppm males at 24 months and increased absolute and relative adrenal weight at 12 and 24 months in both sexes.

Histopathology

Histopathological changes that appeared to be compound related are summarized in Table C, 12 month sacrifice and Table D, 24 month sacrifice. At 12 months treatment related effects were confined to the eyes and the small intestine. Ocular effects consisted of retinal atropy in all high dose males and females. The unique character of this pathology is described below in relation to the 24 month sacrifice. In the small intestine autolysis was observed in all groups and vacoular degeneration, in a dose related fashion, in the 40 and 320 ppm groups ($p \leq 0.05$ at 320 ppm).

Effects on the retina and the small intestine were also observed at the 24 month sactifice. Intestinal effects consisted of autolysis, vacoular degeneration and hyperplasia; all dose related and statistically significant at 320 ppm ($p \leq 0.05$).

"Retinal atrophy, in the 320 ppm groups, was characterized microscopically by diffuse loss (disappearance) of most of the outer layers of the retina, including the layer of rods and cones, outer limiting membrane (assumed), the outer nuclear layer, the outer plexiform layer, and sometimes portions of the inner nuclear layer. The pigment epithelium, considered anatomically to be the outermost retinal layer, was present, but contained increased eosinophilic granular to flocculent cytoplasmic material which was of sufficient quantity to distort the cell in some instances. The coroid was reduced in thickness in approximate relation to the thickness of the remaining retina; it appeared functional in terms of patency of vessels and the presence of blood. The layer of optic nerve fibers and the ganglion cell layer were sometines reduced in thickness, but this was variable in occurence."

"In the typical presentation at either one or two years, the appearance was of diffuse loss of the rods and cones, outer limiting membrane, outer nuclear layer and outer plexiform layer, with "collapse" of the remaining inner layers onto the pigment epithelium. Occasional darkstaining nuclei, remnents of the outer nuclear layer, could be noted at the edge of the remaining inner nuclear layer. In the extreme presentation, the inner nuclear layer was also affected, with gaps in the layer and distrotions of the normal layered appearance (i.e., it demonstrated a dysplastic appearance) and more thinning of the layer than in the control or less affected animals."

"The retinal changes in the 320 ppm animals were essentially confined to that group by virtue of being diffuse and bilateral, and by some evidence that the lesion started in the central portion of the retina. In several 320 ppm rats which died prior to one year on study, but later than three months on study, early outer segmental degeneratin could be

detected in the central portions of the retina. There was no change apparent in the 320 ppm animals which died [immediately] following the three month bleeding interval."

"The frequency of diffuse, bilateral retinal atrophy at one year was: (M-0/20, 0/10, 0/10, 19/20*; F-0/20, 0/10, 0/10, 20/20*); in two year rats: (M-1/50, 0/50, 0/50, 50/50*; F-0/50, 2/50, 0/50, 40/50*)." [*$p \leq 0.05$]

"Retinal atrophy in other groups, including the control, was clearly differentated from the lesion in the 320 ppm groups in several ways:

1. Most occurances of atrophy at two years were peripheral in distribution; there were several instances at one year also. This change is characterized by thining of the portion of the retina near the ciliary body, and is considered an aging change: a one year (M-1/20, 0/10, 1/10, 0/20; F-1/20, 1/10, 0/10, 0/20); at two years: (M-11/50, 15/50, 21/50, 0/50*; F-30/50, 33/50, 36/50, 0/50*)." [*$p \leq 0.05$]

2) Most occurances were unilateral atrophy, which was usually related to an inflamatory change or other lesions: at one year (M-4/20, 1/10, 3/10, 1/20; F-4/20, 3/10, 1/10, 0/20); at two years: (M-11/50, 15/50, 18/50, 0/50*; F-21/50, 24/50, 18/50, 0/50*). The peripheral lesions taken as a group tended to be unilateral as well: all at one year and at two years (M-6/50, 9/50, 13/50, 0/50*; F-17/50, 19/50, 15/50, 0/50*). There was no bilateral retinal atrophy in control, 4, or 40 ppm groups at one year; there was a small proportion in those groups at two years (M-5/50, 6/50, 8/50, 50/50*; F-13/50, 16/50, 21/50, 41/50*)." [*$p \leq 0.05$]

3) Electroretinography showed essenially complete loss of retinal response on stimulation in the 320 ppm group and normal responses in the other treated groups. This confirmed the microscopic impressions of compound effect in the 320 ppm groups only."

Additional histopathology of the eye seen at 24 months consisted of uveitis, cataract and neovasclarization in both sexes and statistically significant at 320 ppm. A statistically significant increase in atropy of the optic nerve was observed in both sexes at 320 ppm.

In the adrenals, a statistically significant increase in vacoular degeneration was observed in both sexes at 320 ppm.

A curious response to treatment were decreases in chornic nephropathy of the kidneys, billary hypertrophy/fibrisis of

the liver, testicular atropy, and degerenative/fibrous myopathy of the heart.

No dose related increases in tumor incidence were observed. In the females incidence of mononuclear cell leukemia was decreased, in a dose related manner, in the kidneys and the spleen.

No treatment related effects on the nervous system were observed in the neurotoxicity animals.

102675

Table AI-MEAN

Average Intake of Active Ingredient (Tribufos) over the Entire Study Period of Two Years

Study 88-271-AA

Sex	Doses (ppm in the feed) Nominal	Doses (ppm in the feed) Actual[1]	Mean[2] Feed Consumption (g/kg b.wt./day)	Mean Intake[3] of Active Ingredient (mg AI/kg b.wt./day)
Males	0	0.0	47.6 ± 1.0	0.0
	4	4.0 ± 0.2	47.4 ± 1.0	0.2
	40	38.5 ± 1.2	47.9 ± 0.9	1.8
	320	326.0 ± 9.0	51.6 ± 0.7	16.8
Females	0	0.0	59.3 ± 0.9	0.0
	4	4.0 ± 0.2	58.9 ± 0.9	0.2
	40	38.5 ± 1.2	59.7 ± 0.9	2.3
	320	326.0 ± 9.0	64.8 ± 0.6	21.1

[1] Actual dosages were verified analytically with each value representing the mean ± standard error (SE) of nine separate determinations.

[2] Each value represents the mean ± SE of at least 100 weekly group means determined over the course of the entire study.

[3] Actual dose level (ppm/1000) x mean feed consumption (g/kg body weight/day) = mean intake of the active ingredient (mg tribufos consumed/kg body weight/day).

Table A. Mean body weight and survival of males at 4 week intervals. Oncogenic animals
Data from Table BW-MEAN of the report.

DAY	0	28	56	84	112	140	168	196	224	252	280	308	336	364
Control	139.9	250.6	293.7	309.5	336.0	346.5	364.0	376.2	382.3	290.8	398.8	402.3	408.0	421.6
SD	11.8	11.8	14.1	18.4	19.6	18.0	21.0	21.3	21.0	23.9	25.3	22.1	23.6	25.0
n	60	60	50	50	50	50	50	50	50	50	50	50	50	50
4 ppm	144.9	251.0	295.2	309.8	339.6	352.3	362.4	372.8	380.3	392.0	400.7	405.2	411.1	420.1
SD	12.6	14.2	16.9	18.2	16.8	23.3	19.8	20.2	18.9	20.1	20.7	21.4	21.7	24.0
n	60	60	50	50	50	50	50	50	50	50	50	50	49	49
40 ppm	150.2*	247.4	286.6	296.9*	326.5*	337.4*	348.5*	360.9*	368.4*	378.7*	386.7*	394.2	399.6	406.5*
SD	13.0	12.7	17.8	18.8	17.1	17.8	17.8	17.5	18.0	19.0	19.1	19.8	21.3	21.5
n	60	60	50	50	50	50	50	50	50	50	50	50	50	50
320 ppm	152.5*	213.7*	252.6*	267.6*	293.5*	305.3*	314.0*	321.5*	327.7*	337.1*	344.5*	348.8*	351.1*	355.5*
SD	14.4	17.9	17.3	19.3	17.9	15.3	15.6	15.7	15.3	15.3	17.0	16.9	17.2	18.7
n	60	60	50	50	50	50	50	50	50	50	50	50	50	50

DAY	392	420	448	476	504	532	560	588	616	644	672	700	721
Control	429.1	431.8	438.3	437.1	436.1	435.0	430.9	434.2	426.8	423.6	410.5	399.1	378.9
SD	26.3	26.7	25.7	24.7	25.9	24.7	25.1	27.2	32.3	32.0	32.7	31.5	36.8
n	50	50	50	50	49	49	49	49	46	43	41	37	35
4 ppm	427.4	420.6	429.3	425.8	424.4	422.6	419.9	432.3	421.6	423.3	411.0	406.8	386.2
SD	25.1	29.4	23.8	29.3	31.2	29.1	41.7	28.5	45.1	46.5	29.5	33.6	27.7
n	49	49	48	48	48	47	47	43	43	39	35	32	28
40 ppm	415.9*	418.7*	424.3*	422.4*	421.0*	416.7*	416.7*	417.6*	414.4	409.5	395.5	387.9	376.8
SD	21.3	20.5	21.5	21.3	21.6	20.2	21.2	24.6	28.1	20.5	29.9	27.9	23.5
n	50	50	50	49	49	49	49	49	48	43	42	38	31
320 ppm	359.9*	360.6*	364.1*	365.1*	361.0*	358.3*	358.5*	356.5*	353.0*	349.5*	338.5*	339.0*	322.7*
SD	19.1	19.7	19.5	20.3	25.3	20.4	21.8	22.7	23.7	26.0	29.4	24.8	28.0
n	50	50	50	50	50	50	50	49	47	44	42	34	30

SD standard deviation
n number of animals surviving on the day of weighing
*$p \leq 0.05$

Table B. Mean body weight and survival of females at 4 week intervals. Oncogenic animals. Data from Table BW-MEAN of the report.

DAY	0	28	56	84†	112	140	168	196	224	252	280	308	336	364
Control	110.9	152.3	170.7	175.8	188.5	195.8	202.6	205.1	206.2	208.7	211.5	214.3	216.6	229.3
SD	5.6	7.2	8.1	10.5	8.4	7.9	8.7	8.9	8.7	8.9	9.8	10.5	9.5	10.2
n	60	60	50	48	48	48	48	48	48	48	48	48	48	48
4 ppm	113.9*	153.2	171.8	175.8	191.7	198.6	200.6	204.5	209.1	211.4	214.5	217.3	221.9	229.7
SD	5.6	6.3	9.2	9.7	8.7	8.6	8.8	8.8	9.4	10.2	9.9	13.2	12.4	13.5
n	60	60	50	50	50	50	50	50	50	50	50	50	50	50
40 ppm	116.1*	151.0	167.8	172.0	188.0	192.7	194.8*	200.8	203.3	205.6	208.4	211.5	217.0	223.3*
SD	5.4	7.2	7.9	9.5	9.2	9.3	9.2	10.0	9.6	10.3	10.2	10.3	12.3	12.6
n	60	59	50	48	48	48	48	48	48	48	48	48	48	48
320 ppm	117.3*	144.0*	158.8*	160.8*	174.2*	178.0*	181.2*	185.5*	187.6*	189.9*	193.0*	197.5*	200.8*	206.8*
SD	5.5	6.9	8.9	11.5	9.9	9.9	9.8	10.1	9.9	9.6	9.2	9.9	10.0	12.1
n	60	60	50	45	45	45	45	43	43	43	43	43	43	43

DAY	392	420	448	476	504	532	560	588	616	644	672	700	721
Control	235.9	242.2	249.6	253.2	258.5	264.5	263.2	275.2	276.1	279.5	280.9	275.3	274.3
SD	12.9	14.3	15.3	16.1	18.0	19.0	17.1	19.4	20.0	23.7	22.2	24.4	24.3
n	48	48	48	48	48	48	48	47	46	43	42	41	40
4 ppm	237.2	239.7	246.2	249.4	252.6	261.9	264.1	266.8	274.7	276.8	278.2	279.5	273.9
SD	15.0	16.6	18.0	17.6	19.4	18.6	18.4	20.5	22.0	23.3	24.0	26.8	24.7
n	50	50	50	50	49	48	47	46	44	43	42	41	38
40 ppm	231.2	234.9	242.9	245.5	249.7	252.8*	252.1*	259.6*	266.0	271.0	273.7	169.9	264.3
SD	15.2	17.6	18.2	17.7	19.6	20.7	21.1	22.8	23.4	25.0	26.4	21.9	17.7
n	48	48	48	48	48	46	45	43	43	42	41	36	34
320 ppm	211.5*	212.2*	218.2*	219.3*	221.4*	226.9*	230.4*	234.8*	236.1*	236.3*	236.2*	243.5*	237.1*
SD	12.5	15.3	15.5	16.4	18.2	20.5	21.7	17.8	18.1	19.2	27.7	17.4	14.3
n	43	43	43	43	42	42	40	39	37	37	36	32	30

SD standard deviation
n number of animals surviving on the day of weighing
* $p \leq 0.05$
† animals lost within 24 hours of routine bleeding.

Chronic Oncogenicity/Neurotoxicity Study of Tribufos in Rats
MOBAY Toxicology Department
Study : 88-271--AA CC2-SUM
Species : Rat CHOLINESTERASE SUMMARY
All subsets MALES Page : 1

MEAN Serum Chemistry

Nominal days in study		84			175			350	
MALES		PChe IU/ml	RChe IU/ml		PChe IU/ml	RChe IU/ml		PChe IU/ml	RChe IU/ml
0 PPM/COCNTL	Mean	0.51	2.91	Mean	0.62	3.10	Mean	0.80	2.76
	SD	0.05	0.08	SD	0.05	0.10	SD	0.17	0.16
	n	20	20	n	20	20	n	20	20
4 PPM /L-1	Mean	0.52	2.89	Mean	0.64	3.07	Mean	0.78	2.69
	SD	0.04	0.10	SD	0.04	0.12	SD	0.09	0.09
	n	20	20	n	20	20	n	20	20
40 PPM /L-2	Mean	0.44*	1.87*	Mean	0.49*	2.73*	Mean	0.57*	1.94*
	SD	0.05	0.09	SD	0.03	0.15	SD	0.08	0.11
	n	20	20	n	20	20	n	20	20
320 PPM/L-3	Mean	0.26*	1.32*	Mean	0.31*	1.39*	Mean	0.33*	1.20*
	SD	0.02	0.03	SD	0.04	0.04	SD	0.06	0.09
	n	20	20	n	20	20	n	20	20

Statistics: Anova + Dunnetts tests (two-sided): * P≤0.05 (Exp.Unit = Animal)

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Brain Cholinesterase

Nominal days in study		539			714		Nominal days in study	721
MALES		PChe IU/ml	RChe IU/ml		PChe IU/ml	RChe IU/ml	MALES	
0 PPM/COCNTL	Mean	1.09	2.74	Mean	1.26	2.70	0 PPM/COCNTL	Mean 12.6
	SD	0.31	0.17	SD	0.49	0.20		SD 0.6
	n	20	20	n	20	20		n 20
4 PPM /L-1	Mean	0.87*	2.64	Mean	1.06*	2.71	4 PPM /L-1	Mean 12.8
	SD	0.20	0.23	SD	0.13	0.19		SD 0.5
	n	20	20	n	20	20		n 20
40 PPM /L-2	Mean	0.55*	1.72*	Mean	0.56*	1.98*	40 PPM /L-2	Mean 12.5
	SD	0.10	0.13	SD	0.07	0.12		SD 0.6
	n	20	20	n	20	20		n 19
320 PPM/L-3	Mean	0.33*	0.86*	Mean	0.26*	1.40*	320 PPM/L-3	Mean 5.0*
	SD	0.07	0.13	SD	0.03	0.04		SD 0.9
	n	20	20	n	20	20		n 20

Statistics: Anova + Dunnetts tests (two-sided): * P≤0.05 (Exp.Unit = Animal)

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Chronic Oncogenicity/Neurotoxicity Study of Tribufos in Rats
MOBAY Toxicology Department
Study : 88-271--AA
Species : Rat
All subsets

CC2-SUM
CHOLINESTERASE SUMMARY
FEMALES

MEAN Serum Chemistry

Nominal days in study		84 PCho IU/ml	84 RCho IU/ml	175 PCho IU/ml	175 RCho IU/ml	350 PCho IU/ml	350 RCho IU/ml
FEMALES							
0 PPM/COCNTL	Mean	2.39	2.87	2.92	2.88	3.05	2.56
	SD	0.17	0.07	0.22	0.16	0.24	0.15
	n	20	20	20	20	20	20
4 PPM /L-1	Mean	2.20*	2.78*	2.63*	2.73*	2.73*	2.18*
	SD	0.21	0.07	0.39	0.22	0.33	0.25
	n	20	20	20	20	20	20
40 PPM /L-2	Mean	0.98*	1.81*	1.11*	2.59*	1.11*	1.66*
	SD	0.11	0.08	0.11	0.17	0.18	0.19
	n	20	20	20	20	20	20
320 PPM/L-3	Mean	0.45*	1.35*	0.51*	1.40*	0.48*	1.06*
	SD	0.06	0.06	0.04	0.05	0.10	0.10
	n	20	20	20	20	20	20

Statistics: Anova + Dunnetts tests (two-sided): * P≤0.05 (Exp.Unit = Animal)

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Brain Cholinesterase

Nominal days in study		539 PCho IU/ml	539 RCho IU/ml	714 PCho IU/ml	714 RCho IU/ml	Nominal days in study 721
FEMALES						FEMALES
0 PPM/COCNTL	Mean	2.91	2.51	2.35	2.62	0 PPM/COCNTL Mean 12.9
	SD	0.36	0.16	0.20	0.21	SD 0.7
	n	20	20	20	20	n 20
4 PPM /L-1	Mean	2.73	2.53	2.21*	2.66	4 PPM /L-1 Mean 12.7
	SD	0.55	0.26	0.26	0.13	SD 0.6
	n	20	20	20	20	n 21
40 PPM /L-2	Mean	1.26*	1.57*	0.95*	1.80*	40 PPM /L-2 Mean 12.5
	SD	0.11	0.11	0.10	0.06	SD 0.6
	n	20	20	20	20	n 20
320 PPM/L-3	Mean	0.61*	0.93*	0.41*	1.38*	320 PPM/L-3 Mean 4.1*
	SD	0.15	0.13	0.08	0.04	SD 0.6
	n	20	20	20	20	n 20

Statistics: Anova + Dunnetts tests (two-sided): * P≤0.05 (Exp.Unit = Animal)

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Table C. Selected histopathology from the 12 month intrim sacrifice.
Data from Table GP2-SUM-INT

	0 ppm	4 ppm	40 ppm	320 ppm
MALES				
ADRENALS				
Degeneration, vacoular	17/20(85%)	7/10(70%)	9/10(90%)	20/20(100%)
EYES				
atropy(retinal)	4/20(20%)	1/10(10%)	3/10(30%)	20/20(100%)*
SMALL INTESTINE				
autolysis	6/20(30%)	3/10(30%)	2/10(20%)	3/20(15%)
degeneration, vacoular			7/10(70%)	18/20(90%)*
FEMALES				
ADRENALS				
Degeneration, vacoular				1/20(5%)
EYES				
atropy(retinal)	4/20(20%)	3/10(30%)	1/10(10%)	20/20(100%)*
cataract	2/20(40%)	1/10(10%)		1/20(5%)
SMALL INTESTINE				
autolysis	6/20(30%)	3/10(30%)	2/10(20%)	9/20(45%)
degeneration, vacoular			8/10(80%)	16/20(80%)*

number observed/number examined
* $p<0.05$

Table D. Selected histopathology from the 24 month sacrifice. Data from Table GP1-SUM from the report.

010119

	0 ppm	4 ppm	40 ppm	320 ppm
MALES				
ADRENALS				
Degeneration, vacoular	6/50(12%)	6/49(12%)	9/50(18%)	35/49(71%)*
EYES				
atropy(retinal)	17/50(34%)	21/50(42%)	26/50(52%)	50/50(100%)*
uveitis	1/50(2%)	1/50(2%)		15/50(30%)*
cataract	9/50(18%)	6/50(12%)	9/50(18%)	50/50(100%)*
neovasclarization	7/50(14%)	7/50(14%)	5/50(10%)	16/50(32%)*
KIDNEYS				
chronic nephropathy	50/50(100%)	50/50(100%)	46/50(92%)	34/50(68%)
microlith			1/50(2%)	9/50(18%)
LIVER				
Hyper./fibr.,billary	36/50(72%)	31/50(62%)	15/50(30%)	1/50(2%)*
Hyo. focal,hep.	12/50(24%)	6/50(12%)	3/50(6%)	2/50(4%)
OPTIC NERVES				
atropy	10/50(20%)	6/50(12%)	6/50(12%)	32/49(65%)*
SMALL INTESTINE				
autolysis	4/50(8%)	8/50(16%)	15/50(30%)	13/50(26%)*
degeneration, vacoular		1/50(2%)	24/50(48%)	37/50(74%)*
hyperplasia		3/50(6%)	23/50(46%)	34/50(68%)*
TESTES				
atropy	11/50(22%)	16/50(32%)	4/50(8%)	6/50(12%)
interst. cell tumor	47/50(94)	41/50(82%)	48/50(96%)	50/50(100%)
FEMALES				
ADRENALS				
Degeneration, vacoular	10/50(20%)	6/50(12%)	16/50(32%)	41/49(82%)*
EYES				
atropy(retinal)	34/49(69%)	40/50(80%)	38/50(76%)	42/50(84%)
uveitis	5/49(10%)	5/50(10%)	7/50(14%)	22/50(44%)*
cataract	5/49(10%)	8/50(16%)	8/50(16%)	41/50(82%)*
neovasclarization	14/50(28%)	15/50(30%)	9/50(18%)	23/50(46%)*
HEART				
deg/fibr(C'myopathy)	43/50(86%)	36/50(72%)	37/50(74%)	28/50(56%)*
KIDNEYS				
chronic nephropathy	39/50(78%)	45/50(90%)	30/50(60%)	25/50(50%)*
leuk.,mononuc.cell	4/50(8%)	3/50(6%)	2/50(4%)	1/50(2%)
LIVER				
Hyper./fibr.,billary	13/50(26%)	17/50(34%)	6/50(12%)	1/50(2%)*
OPTIC NERVES				
atropy	15/50(30%)	12/50(24%)	12/50(24%)	34/49(68%)*
SMALL INTESTINE				
autolysis	10/50(20%)	14/50(28%)	19/50(38%)	16/50(32%)
degeneration, vacoular			19/50(38%)	35/50(70%)*
hyperplasia	1/50(2%)		11/50(22%)	30/50(60%)*
SPLEEN				
leuk.,mononuc cell	21/50(42%)	21/50(42%)	12/50(24%)	6/50(12%)*

number observed/number examined

* $p<0.05$

13544

028246

Chemical:	~~Sulfonium, trimethyl-, salt with N-(phos—~~
PC Code:	~~128501~~ 074801
HED File Code	13000 Tox Reviews
Memo Date:	*03/24/93*
File ID:	TX010119
Accession Number:	412-02-0011

HED Records Reference Center
03/01/2002